BONE MARROW IMAGING USING ^{111}In-CITRATE: ^{111}In-KINETICS IN THE PELVIC REGION

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When bone marrow scintigraphy was performed using ^{111}In-citrate, radioactivity was observed in the pudendal region. Subsequently, the kinetics of ^{111}In in the pelvic region after intravenous administration of ^{111}In-citrate for bone-marrow scanning in 14 patients was examined. On the first day, radioindium was found predominantly in the large pelvic blood vessels and in the pudendal region. In all male patients, the scrotal area was affected with both testes presumably delineated in two patients. In the female patients little radioindium was detected in the pudendal region, most probably in the vulva; distinct radioactivity was found in the pelvis although the ovaries could not be identified. In the following period the ^{111}In uptake in the bone marrow increased considerably and reached its maximum usually 24 hr after the injection. Because a distinct radiation dose from ^{111}In to the gonads cannot be excluded on the basis of our scintigraphic findings and the absorbed dose has not yet been estimated sufficiently, judgment should be used for the present if ^{111}In-citrate is applied for bone marrow imaging.

The introduction of ^{111}In-chloride into nuclear medicine offers the advantage that this radioisotope is available carrier-free and gives a high yield of photons with suitable energies for imaging. It was found useful for hematopoietic bone marrow scanning because it was supposed to behave in a manner metabolically similar to that of iron (*1*). Other authors assumed this, at least for normal persons (*2*), or considered scintigraphy with ^{111}In-chloride to be a reliable means of assessing erythroid elements in bone marrow but not in liver and spleen (*3*). Indium-111-chloride was superior to ^{99m}Tc-sulfur colloid (*1,4*) and ^{111}In-citrate proved to be more suitable for a good delineation of morphologic details than ^{99m}Tc-sulfur rhenium colloid (*5*). We prefer bone marrow imaging with ^{111}In-citrate owing to its more physiologic pH in comparison with the acid pH of ^{111}In-chloride.

When, by chance, we performed bone marrow scintigraphy after intravenous administration of ^{111}In-citrate, we noticed radioactivity in the pelvic region during the first hours. This finding prompted us to observe the kinetics of ^{111}In when we used it for bone marrow scanning.

PATIENTS AND METHODS

We examined ten men and four women, aged 38–60 years. Eleven of these patients suffered from end-stage renal failure treated by hemodialysis. We assumed that the impairment of their renal function might delay the ^{111}In retention in the total body, enhance the uptake by the bone marrow, and make a partial removal of the radioisotope possible by rapid hemodialysis. One man suffered from iron deficiency anemia (under treatment) and another from essential hypertension. In one woman the diagnosis was uncertain.

We carried out rectilinear scintigraphy after intravenous administration of 2–5 mCi of carrier-free ^{111}In-citrate as a sterile solution in isotonic citrate buffer at pH 5–8. We are grateful to the supplier (The Radiochemical Centre, Amersham, England) for information about the purity of the product. Scanning was performed usually 1, 3, and 5 hr after the injection as well as in the following 2–11 days, daily or at intervals of 1–3 days. The scans covered the field from the lower lumbar spine to the proximal part of the femur and, if necessary, the lower leg. The patients were examined both in prone and supine

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position after they had been asked to void. We used a FH 807 B 5-in. scanner (Berthold/Frieseke GmbH) equipped with a 5-in. focal depth high-energy collimator. Under appropriate calibration the background subtraction amounted to approximately 10%.

RESULTS

In all patients radioindium was found in the pudendal region to an individually variable extent. The following five examples may be considered to be representative of our findings.

In a 60-year-old man, suspected of having a hematologic disease and in whom hematologic findings proved to be normal later, the scan 5 hr after the administration of ^{111}In-citrate showed a high amount of radioactivity in the large pelvic blood vessels, the urinary bladder, the penis, and most probably the testes (Fig. 1, left). After 8 hr radioindium in the large pelvic blood vessels and the pudendal region had decreased although very probably both testes were still delineated. The bone marrow contained relatively little ^{111}In (Fig. 1, right). After 2 days radioactivity could still be detected distinctly in the pudendal region, presumably also in both testes; meanwhile there had been a relative increase in ^{111}In uptake in the bone marrow (Fig. 2, left).

In a 46-year-old man with essential hypertension, much radioindium was observed rapidly in the large pelvic blood vessels and in the scrotal area; at 2 hr a large quantity of ^{111}In was detected (Fig. 2, right). The testes were not demarcated and the bone marrow contained little radioactivity. After 24 hr the bone marrow was delineated and the pudendal region, particularly the scrotal area, had lost most of its radioindium so that it was only faintly visualized.

In a 57-year-old man under treatment for iron deficiency, radioactivity was found in the pudendal region as well as in the bone marrow (Fig. 3, left) by 2 hr after injection of ^{111}In-citrate. At 18 hr still more ^{111}In had accumulated in the bone marrow whereas the amount of radioactivity in the pudendal region had decreased, leaving it open to question whether there was some ^{111}In in the testes (Fig. 3, right). After 44 hr the radioactivity in the pelvic region was reduced but possibly there was a small quantity of ^{111}In in the testes (Fig. 4, left).

In a 38-year-old man with end-stage renal failure, a large quantity of radioindium was seen after 3 hr both in the large pelvic blood vessels and the pudendal region, mainly the scrotal area. After 1 day the bone marrow, the urinary bladder, and the pudendal region could be recognized well whereas the testes were not distinguishable. In the pelvic blood vessels considerable radioactivity was still present. After 4 days morphologic details of the bone marrow continued to be well delineated. The pudendal region, especially the scrotal area, contained less ^{111}In. After 6 days the quantity of radioindium in the pudendal region was reduced more than that in the bone marrow. After 11 days the amount of ^{111}In in the pelvic region had decreased further.

A 50-year-old woman with a still uncertain diagnosis showed a marked quantity of radioindium in the large pelvic blood vessels 3 hr after the administration of ^{111}In-citrate (Fig. 4, right). Little radioindium was detected in the pudendal region and apparently some in the vulva. After 24 hr considerable radioactivity was found in the bone marrow, the urinary bladder, and probably in other organs of the pelvic region. These organs, however, could not be identified; the ovaries might have been among them.

DISCUSSION

The kinetic studies confirmed our observations in 11 patients (*6*) in whom ^{111}In was detected in the pudendal region after intravenous administration of ^{111}In-citrate. Moreover, the results are an argument for uptake of radioindium in pelvic organs. The ^{111}In kinetics in the first 6–24 hr were characterized by a high amount of radioactivity in the large pelvic blood vessels and in the pudendal region, chiefly the scrotal area. Possibly the pudendal region contains much radioindium in smaller blood vessels. Probably the injection of ^{111}In-citrate leads to a rapid binding of ^{111}In to transferrin as was reported for ^{111}In-chloride (*4,7*). The ^{111}In-labeled transferrin appears to leave the blood vessels slowly and at a rate that is variable in patients suffering from different diseases. Nevertheless, it is uncertain whether the speed of the ^{111}In transfer from the blood vessels to the tissues has some relation to certain diseases and might be due, at least partly, to a variable avidity of certain tissues for radioindium administered as ^{111}In-citrate. Perhaps in the patient with iron deficiency anemia or with essential hypertension the avidity of tissues for ^{111}In is stronger than in most of the patients suffering from end-stage renal failure in whom a decreased erythropoiesis may be assumed.

Because the renal excretion of radioindium was high, the urinary bladder was usually visible in the first hours after the administration of ^{111}In-citrate, even shortly after the bladder was emptied. All male patients showed an individually variable quantity of radioindium in the pudendal region, particularly in the scrotal area. In two men both testes were presumably delineated. In five men the penis was demarcated, perhaps owing to its high vascularization. In all four female patients a distinct amount of ^{111}In was observed in the pudendal region, mainly in the

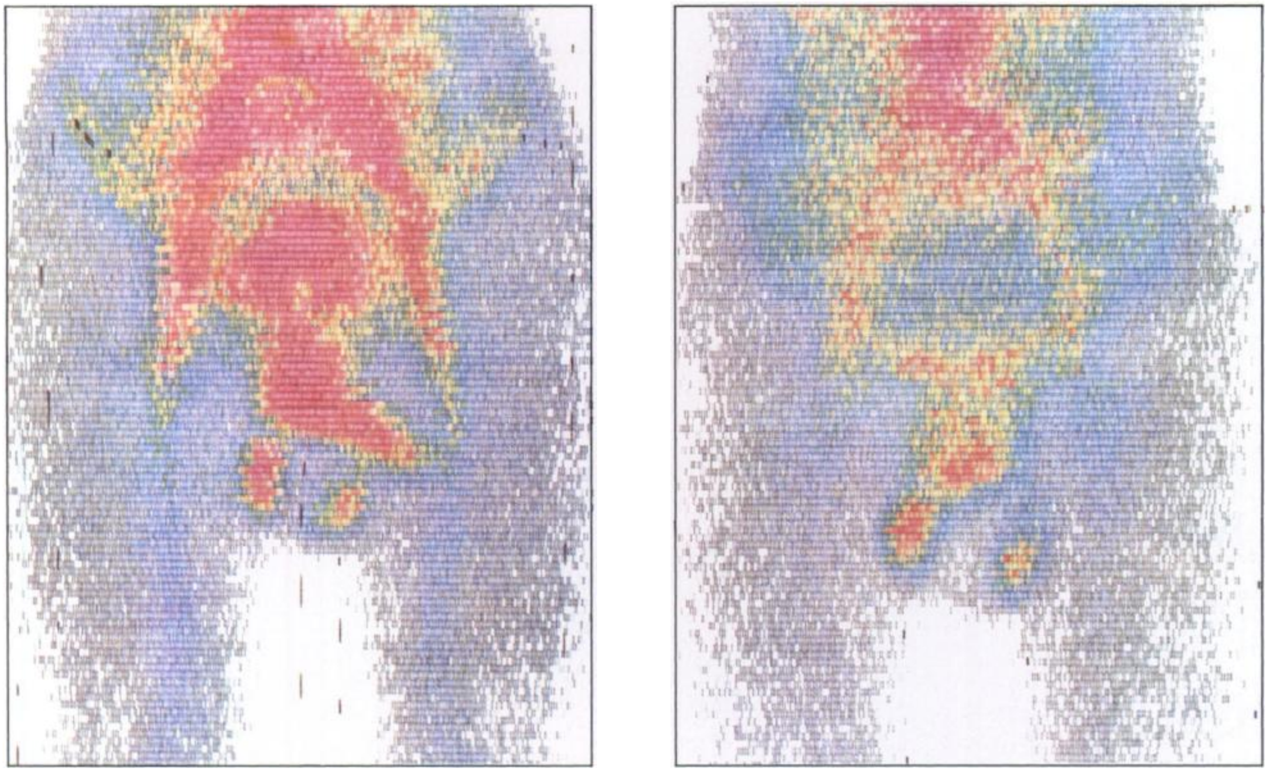

FIG. 1. Left: anterior view of 60-year-old man shows high amount of ^{111}In in large pelvic blood vessels, penis, and most probably testes, after 5 hr. Right: anterior view after 8 hr reveals less ^{111}In in pelvic region (in comparison with scan after 5 hr).

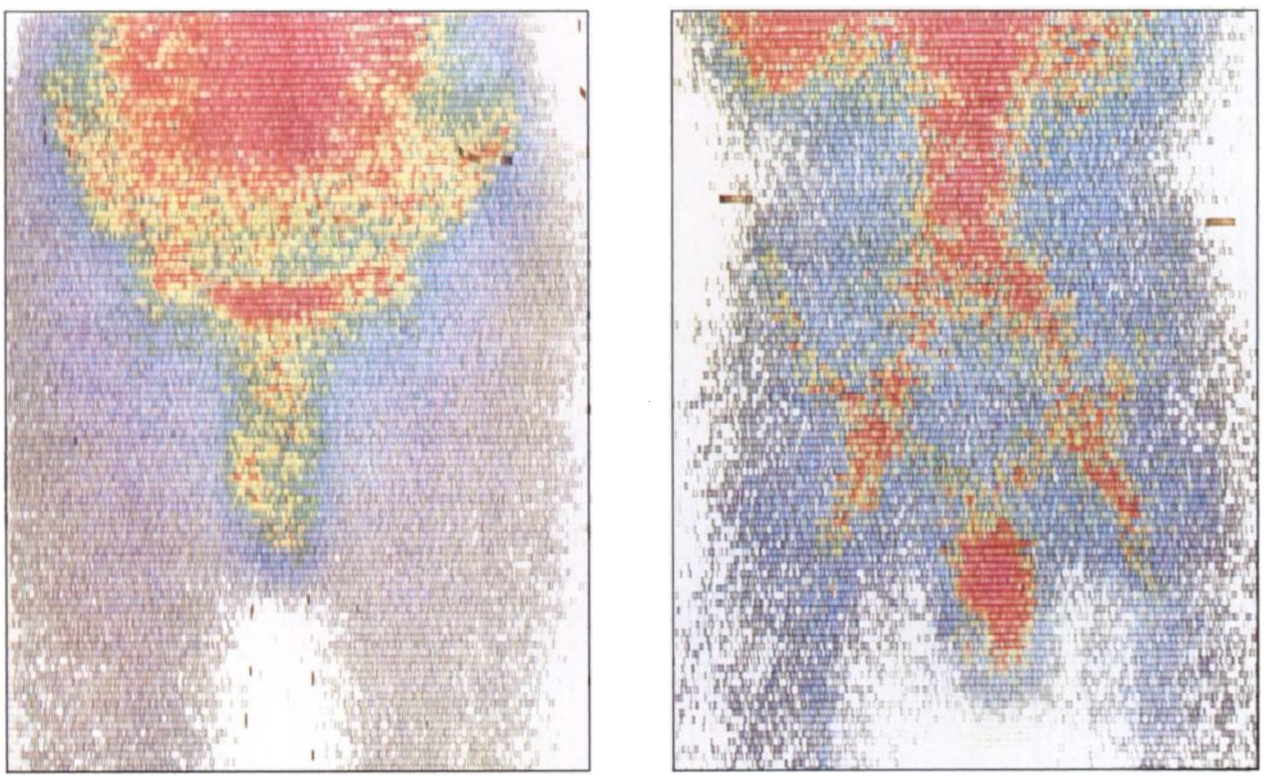

FIG. 2. Left: in anterior view of 60-year-old man (Fig. 1) ^{111}In has increased in bone marrow but diminished in pudendal region after 2 days. Right: anterior view of 46-year-old man shows high amount of ^{111}In in large pelvic blood vessels and penis after 2 hr.

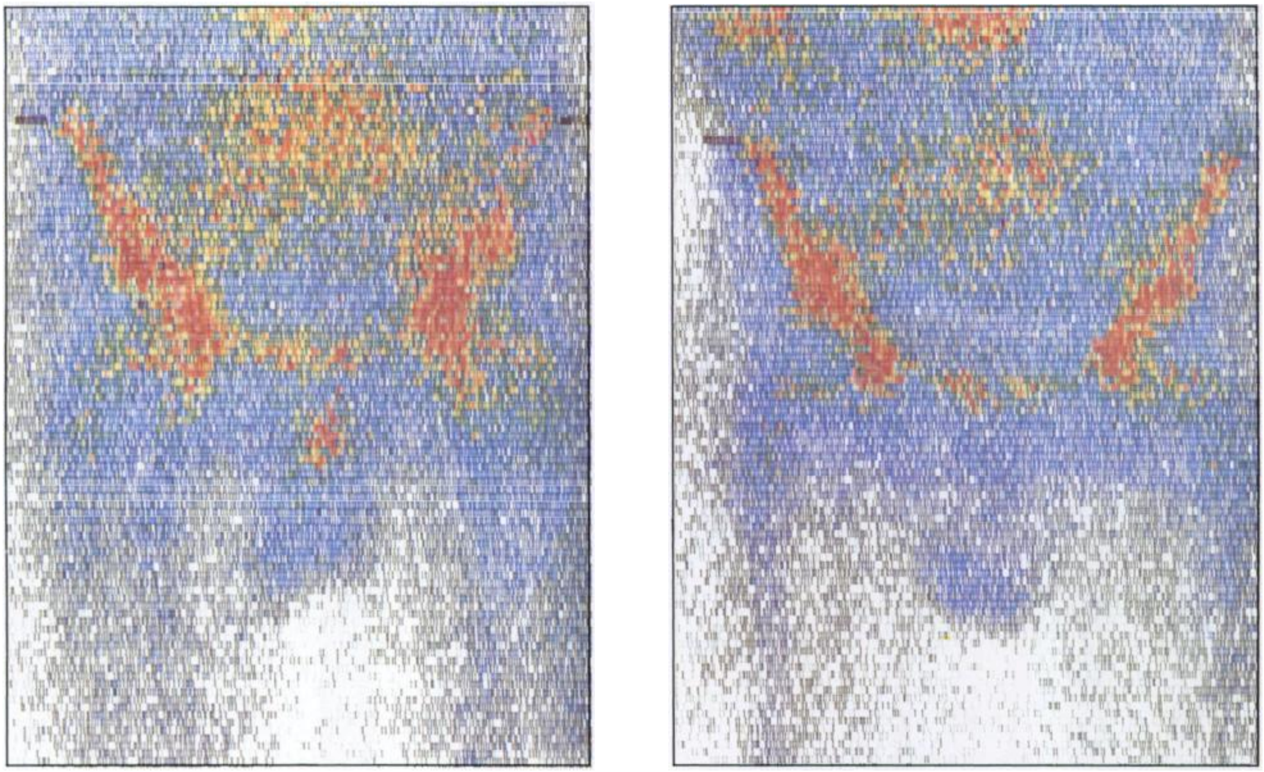

FIG. 3. Left: anterior view of 57-year-old man shows high ^{111}In uptake in bone marrow and pudendal region after 2 hr but comparatively little radioindium in large pelvic blood vessels. Right: in anterior view after 18 hr ^{111}In has increased in bone marrow and diminished in pudendal region; uptake of ^{111}In in testes cannot be excluded.

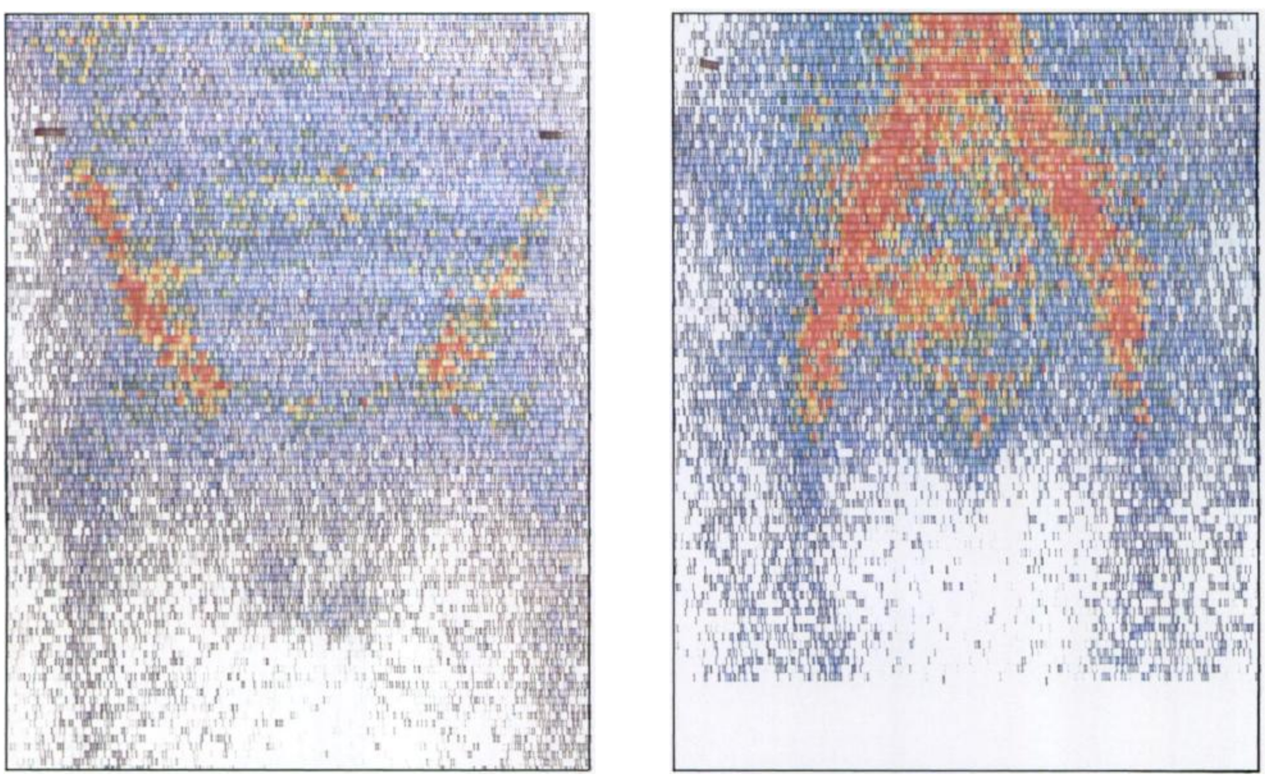

FIG. 4. Left: anterior view in 57-year-old man (Fig. 3) demonstrates decrease of ^{111}In in pelvic region after 44 hr; possibly there is some radioindium in testes. Right: in anterior view of 50-year-old woman considerable ^{111}In is found in large pelvic blood vessels, little is found in pudendal region, and apparently some in vulva after 3 hr.

vulva. The ovaries could not be distinguished. The pudendal region of the female patients, however, contained only a small quantity of radioindium in a rather homogeneous distribution during the first day.

About 6–24 hr after the administration of ^{111}In-citrate, the accumulation of radioactivity in the bone marrow increased. As was shown for transferrin-bound iron, transferrin-bound indium was probably incorporated into erythroid precursors in the bone marrow (*1,4,7*). The ^{111}In uptake is considered to be evidence of the sites of red cell production in the bone marrow and also an indication of extramedullary erythropoiesis in the spleen (*2*). The amount of ^{111}In in the bone marrow and other organs probably depends on the avidity of phagocytic or other cells for ^{111}In-citrate (or other ^{111}In compounds derived from it within the body) as well as on the blood flow. This assumption might also explain the fact that in our patients radioindium was detected in the pudendal region, particularly in its highly vascularized organs. We found the most suitable time for bone marrow imaging, especially of the sacrum with the patient lying in prone position, to be between 8 and 24 hr; after 2 days ^{111}In left the bone marrow slowly and to a different extent in each case. It decreased more rapidly in the patient with essential hypertension than in all patients suffering from end-stage renal failure. The impaired renal ^{111}In excretion probably caused a delayed radioindium elimination from the bone marrow and the pudendal region so that in one patient with end-stage renal failure a distinct amount of ^{111}In was found there even after 11 days.

A considerable external contamination from radioindium voided in the urine seems to be less probable because in all patients radioactivity was noticed consistently to the same extent only in the scrotal area and in some patients it even corresponded to the position of the testes. We made no similar observations when using other radioisotopes such as ^{99m}Tc for scintigraphy. The patients did not consent to a biopsy of the testes.

Indium-citrate appears to be a valuable adjunct in obtaining information concerning morphology and function of the bone marrow. The distribution of radioactivity in the bone marrow after intravenous injection of ^{111}In-citrate is not entirely identical with that after intravenous administration of ^{99m}Tc-sulfur rhenium colloid (*5*). A nonidentical distribution is also reported in the comparison of ^{111}In-chloride and ^{99m}Tc-sulfur colloid (*1*). Indium-111-chloride does not label the reticuloendothelial system (RES) or the bone (*4*) primarily. Obviously ^{111}In-chloride does not generally behave like a simple colloid nor is it analogous to iron (*8*). A comparison of ^{52}Fe(II)-citrate and $^{111}InCl_3$ in rabbits favors the view that ^{111}In-chloride might be more practicable for hematopoietic bone marrow scanning than the ^{52}Fe compound (*9*). On the other hand, experimental results in dogs, rats, and rabbits suggest that, with regard to erythropoiesis, the metabolism of indium differs significantly from that of iron so that ^{111}In-transferrin as an agent for bone marrow imaging should be approached with caution (*10*). These findings can be explained by differences of the mechanisms in bone marrow that are involved in the accumulation of radioisotopes such as ^{99m}Tc-sulfur colloid and ^{52}Fe (*11,12*) as well as ^{111}In.

The ^{111}In kinetics after intravenous administration of ^{111}In-citrate used for bone marrow imaging raises the question of the radiation dose. The observation of a distinct amount of ^{111}In in the pudendal region, mainly the scrotal area, sometimes with probable delineation of the testes, should be taken into consideration. The absorbed dose for the bone marrow was assessed to be 7,200 mrads/2 mCi of ^{111}In-chloride as a preliminary value (*1*) but only 300 mrads/10 mCi of ^{99m}Tc-sulfur colloid (*13*). If the metabolism of ^{111}In-citrate is assumed to be similar to that of ^{111}In-chloride, a distinct radiation dose for the gonads cannot be excluded. An estimate of the absorbed dose from either ^{111}In-labeled compound according to the concept of the Medical Internal Radiation Dose (MIRD) Committee (*14,15*) or its extended concept (*16,17*) is not known to us. As long as there is insufficient information on this point, ^{111}In-citrate should be used judiciously for routine bone marrow imaging.

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